Results:

1. **Observed Effects:** Salivation, head shaking, open mouth, partly closed and/or moist eyes and rhinorrhea were seen mainly in high dose groups. Subdued behavior, salivation, licking lips, and pink ears and gums were also seen in the treatment groups.

2. **Mortality:** One control female was sacrificed on day 38 (recovery). Necropsy revealed acute hemorrhagic enteritis.

3. **Body Weights:** The initial and final mean body weights of control group were 6.84 kg and 8.63 kg (males) or 5.99 kg and 7.37 kg (females), respectively. There were no treatment related changes.

4. **Food Consumption:** Food consumptions in control males and females were g/kg/day and g/kg/day respectively. There were no treatment related changes.

5. **Hematology:** Slight increases in leucocytes and neutrophils (~28%) were noted in the high dose females. Monocyte (~36%) and eosinophils (62%) were also increased in the high dose females.

6. **Clinical Chemistry:** Alanine aminotransferase (40.7%) and aspartate aminotransferase (59%) were slightly increased in the treated females. A slight increase in aspartate aminotransferase (22.8%) was also noted in the mid dose females.

7. **Urinalysis:** There were no treatment related changes.

8. **Ophthalmic Examination:** No treatment related effects were seen.

9. **ECG:** There were no treatment related changes.

10. **Organ Weights:** There were no treatment related changes.

11. **Gross Pathology:** No treatment related effects were seen.

12. **Histopathology:** There were no treatment related changes.

13. **Toxicokinetics:** The toxicokinetic data were summarized in a table on page 51 in Volume 34 and this table is attached below.

Summary of toxicokinetic data (sexes combined)

Parameter (units)	1 mg/kg*		3.5 mg/kg*		12.25 mg/kg*	
	Day 1	Day 36	Day 1	Day 36	Day 1	Day 36
C_{max} (ng/mL)	868	722	2820	2950	8610	10010
T_{max} (hour)	0.10	0.08	0.10	0.08	0.15	0.10
$t_{1/2}$ (hour)	0.71	0.57	0.71	0.84	1.20	1.14
AUC_{0-t} (ng.h/mL)	783	504	3370	2900	12500	14900
$AUC_{0-\infty}$ (ng.h/mL)	872	549	3430	3440	12600	14900
CL (mL/min/kg)	20.0	32.6	17.7	17.4	16.9	14.0
Vd_{area} (L/kg)	1.24	1.55	1.15	1.33	1.73	1.38

* expressed as GR68755X

Plasma levels of GR 68755 increased with increasing dosages. There is no indication of accumulation of the drug after repeat administration.

In summary, dogs were treated intravenously with GR 68755 at 0, 1, 3.5, and 12.25 mg/kg/day for 35 or 36 days. The major treatment related changes were clinical signs of toxicity including salivation, head shaking, open mouth, partly closed and/or moist eyes and rhinorrhea, subdued behavior, licking lips, and pink ears and gums (more in the high dose group). Central nervous system was the target organ of toxicity.

35-Days Oral Toxicity Study in Dogs (Study # D 11825)

Testing Laboratories: Pathology and Toxicology Division
Glaxo Group Research Ltd.,
Hertfordshire, UK.

Study Started: April 17, 1989

Study Completed: November 27, 1989

GLP Requirements: A Statement of Compliance with GLP regulations was included.

Animals: Beagle dogs (4-5 months old; males = 7.20-9.95 kg and females = 6.90-8.55 kg).

Drug Batch No.: C1017/69/1 and C1017/77/1.

Methods: In this study dose selection was based on dose-ranging study (# D 11616) in which escalating doses of 5 to 35 mg/kg/day over 32 day period were used in 1 male and 1 female dog. A dose level of 35 mg/kg/day was lethal. A dose level of 30 mg/kg/day was well tolerated dose, however, when given on empty stomach, dogs experience severe reaction such as salivation, inactivity, tremor, lying down, eye half closed, labored respiration and ataxia. The male dog died and the female dog was killed in extremis at 1.5 hr after the drug administration. Based on these findings sponsor selected 30 mg/kg/day as the top dose for the present study and dogs were allowed to eat at least 2 hr prior to drug administration. Groups of dogs (3/sex/group) were given orally (gavage) GR 68755 at daily doses of 0 (vehicle: water), 1, 5.5 and 30 (in females dosage was reduced to 20 mg/kg on day 6 then increased to 25 mg/kg on day 10 and 30 mg/kg from day 12 onwards) mg/kg/day. The volume of administration in control, low dose, mid dose and high dose males was fixed at 1 ml/kg while in high dose females volumes were 2 ml/kg on days 1-5, 1.33 ml/kg on days 6-9, 1.67 ml/kg on days 10 and 11 and 2 ml/kg from day 12 onwards. All dogs were observed for clinical signs twice daily. Body weights were recorded twice weekly and food intakes were recorded weekly. Ophthalmic examinations and ECG recordings were performed on all dogs once pre-test and at the end of study period. Blood samples were collected from jugular vein for hematology and serum chemistry tests at pre-test and on day 16 and 29 of the study. Blood samples were also collected from 2 dogs/sex/group at 0 (before drug administration), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hr after drug administration on days 1/2 and 33/34 of the study for measuring drug levels in plasma according to _____ methods. At the end of study period all surviving dogs were sacrificed and subjected to complete necropsy and histopathological examinations.

Results:

1. **Observed Effects**: Salivation, subdued behavior, vomiting, half-closed eyes and trembling were seen in high dose treated dogs. Subdued behavior was also seen in low and mid dose treated dogs.

2. **Mortality**: One high dose treated male died during study period. Prior to death this dog had severe reaction (lack of coordination, staggering, paleness of the ears and gums, falling, salivation and collapse) to the treatment. Microscopic examination of this dog failed to establish the cause of death.

3. **Body Weights/Food Consumption/Water Consumption**: The initial and final mean body weights of control males were 8.67 kg and 10.28 kg and the corresponding mean weights of control females were 7.50 kg and 8.34 kg respectively. Food consumptions in control males and females were g/kg/ day and g/kg/day respectively. In high dose treated males, body weight gains were reduced by 13.7% compared to control values while high dose treated females lost 8% of their initial weights. Mean food consumptions were decreased by 16% and 22% in high dose treated males and females respectively, when compared to the mean control values.

4. **Hematology/Coagulation/Bone Marrow**: No treatment related effects were seen.

5. **Blood Chemistry/Urinalysis**: Serum creatinine levels were increased by 16% in high dose treated females and 1 out of 2 high dose treated males the cholesterol level was increased by 71% over pre-test value at day 29 of the study.

6. **Vital Signs/Physical Examination/Ophthalmic Examination/ECG**: No treatment related effects were seen.

7. **Organ Weights**: There were only 2 dogs/sex in high dose at the termination of the study, therefore, a meaningful statistical comparison is not possible. Nevertheless, thymus relative weights in high dose group were decreased by 21% and 34% in males and females respectively. Relative liver weights were increased by 22% and 15% in high dose treated males and females respectively. Relative weights of kidneys were increased by 11%, 23% and 31% in low, mid and high dose treated male dogs, when compared to control values.

8. **Gross Pathology**: No treatment related effects were seen.

9. **Histopathology**: Minimal involution of the thymus was seen in 2 out of 3 each high dose treated males and females and 1 out of 3 mid dose treated males.

10. Plasma Level of GR 68755 (Report # WPT/89/247): Plasma levels of GR 68755 increased with increasing dosages in a non-linear fashion. There were no sex differences. This non-linearity resulted in significant increases in $t_{1/2}$ at high dose. Non-linearity in C_{max} and AUC values could be related to saturation of drug metabolizing enzymes. However, at 24 hr after drug administration on days 1 and 33 of the study the levels of GR 68755 were close to detection limit (detection limit: ng/ml), hence there is no indication of accumulation of the drug after repeat administration.

Mean GR 68755 PharmacoKinetic Parameters Following a Repeat Oral Dose of GR 68755C to the Dog (Study D11825)

Parameter	Dose Administered					
	1mg/kg		5.5mg/kg		30mg/kg	
	Day 1	Day 33	Day 1	Day 33	Day 1	Day 33
Cmax (ng/ml)	307 (67)	217 (21)	1420 (277)	1100 (141)	9530 (1310)	7260 (1615)
Tmax (hour)	0.75 (0.2)	0.69-0.75 (0.2-0.3)	0.56 (0.1)	1.4 (0.5)	0.56 (0.3)	1.8 (0.9)
t½ (hour)	0.8	0.8	1.2	0.9	2.6	2.6
AUC(o-t) (ng/ml.h)	498 (175)	255 (76)	3330 (724)	2930 (499)	26500 (4520)	46000 (11100)
AUC(o-∞) (ng/ml.h)	554 (173)	296 (93)	3500 (684)	3040 (474)	27100 (4410)	46500 (10900)

Standard deviation in brackets

Table 2, Pg. 312, Vol. 1.22

In this study target organ of toxicity was thymus. Highest tested dose (30/20/25/30 mg/kg/day) also produced CNS toxicities and death. Mid dose level (5.5 mg/kg/day) could be considered as well tolerated dose since it only produced minimal involution of the thymus in 1 out of 3 male dogs.

6-Month Oral Toxicity Study in Dogs (Study # D11865)

Testing Laboratories: Pathology and Toxicology Division
Glaxo Group Research Ltd.,
Hertfordshire, UK.

Study Started: August 22, 1989

Study Completed: March 27, 1990

GLP Requirements: A Statement of Compliance with GLP regulation was included.

Animals: Beagle dogs (18-28 weeks old; males = 7.0-10.6 kg and females = 5.7-9.4 kg).

Drug Batch No.: C1034/104/1, C1034/98/1, C1034/98/1, C1017/189/1 and C1034/102/1.

Methods: In this study dose selection was based on 35-day oral toxicity study in dogs (see above). Groups of dogs (4/sex/group) were given orally (gavage) GR 68755 at daily doses of 0 vehicle: water), 1, 5.5 and 20 (days 1-3)/30 (days 4-8)/25 (day 9 onwards) mg/kg/day for 28 weeks. The volume of administration was fixed at 2 ml/kg. Additionally, 2 dogs/sex were included in control and high dose group for 21-day recovery study. All dogs were observed for clinical signs twice daily. Body weights were recorded weekly. Food intakes were recorded weekly until day 70 of the study (food and water was available at all times). Due to clinical reaction, from day 71 onwards, food was withdrawn overnight and replaced the following morning prior to dose administration. This regimen was implemented in order to reduce clinical reaction and mortality. Ophthalmic examinations and ECG recordings were performed on all dogs once pre-test, days 92, 94, 95, 96 and 183, 185, 186, 187 and 192 of the study. Hearing acuity tests were performed on 1 dog/sex each of control and high dose groups on day 191 of the study. Blood samples were collected from jugular vein during pre-test, weeks 4, 13 and 26 of the study for hematology and serum chemistry tests. Blood samples were also collected at pre-dose, 45 min, 2 hr and 24 hr after drug administration on days 1, 4, 9, 21, 98, 189 and 193 of the study for measuring drug absorption according to methods. Twenty-four hour urine samples during days 30/31, 93/94 and 184/185 were collected for urinalysis. At end of study period/recovery period all surviving dogs were sacrificed and subjected to complete necropsy and histopathological examinations.

Results:

1. **Observed Effects:** Highest tested dose produced CNS toxicities (subdued behavior, salivation, vocalizing, partly closed eyes, open mouth, ataxia and tremor) in dogs.

2. **Mortality:** One male (# 87960) and 2 females (# 87968 and 87984) from high dose group died during the course of study. Prior to death, two dogs (one male and one female) showed severe CNS toxicities, therefore, death of these two dogs were treatment related. No clinical signs were seen prior to the death of dog # 87984 and microscopic examination could not establish the cause of death of this dog.

3. **Body Weights/Food Consumptions/Water Consumptions:** The initial and final mean body weights of control males were 8.82 kg and 14.54 kg and the corresponding mean weights of control females were 7.81 kg and 11.39 kg respectively. Food consumptions in control males and females were g/kg/day and g/kg/day respectively. At the end of treatment period, body weight gains were reduced by 6% and 13.7% in high dose treated males and females respectively, when compared to control values. There was also an indication of decreased food consumptions in high dose treated dogs.

4. **Hematology/Coagulation/Bone Marrow:** No treatment related effects were seen.

5. **Blood Chemistry/Coagulation/Bone Marrow:** At the end of treatment period plasma alkaline phosphatase levels were increased by 68% and 112% in mid and high dose treated male dogs, while in females the corresponding increases were 34% and 42% when compared to their respective control values. At the end of recovery period plasma alkaline phosphatase levels were still high in high dose treated dogs (males: 175% and females: 38% [only high dose group were used for recovery study]). Additionally, plasma alanine aminotransferase activity was increased by 38% in high dose treated males, compared to control values. No treatment related effects were seen in urinalysis.

6. **Vital Signs/Physical Examination/Ophthalmic Examination/ECG/ Hearing Test:** No treatment related effects were seen.

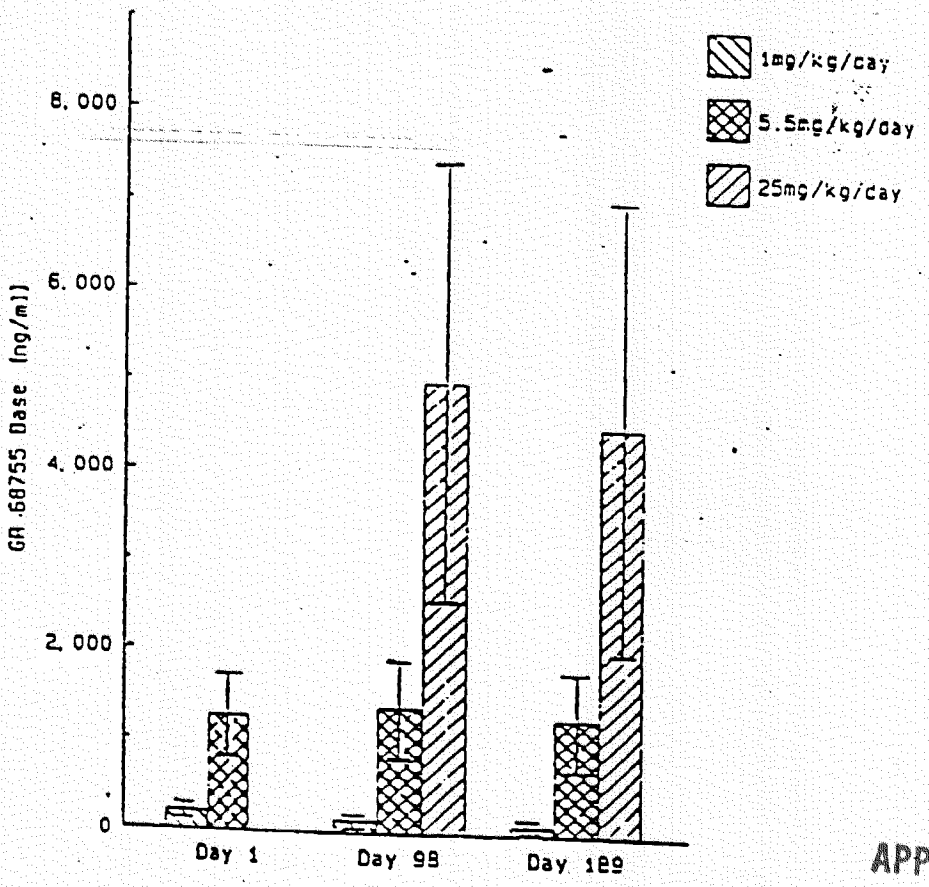
7. **Organ Weights:** No treatment related effects were seen.

8. **Gross Pathology:** No treatment related effects were seen.

9. **Histopathology:** No treatment related effects were seen.

10. Plasma Level of GR 68755 (Report # WPT/90/188): At 45 min (supposedly C_{max}, based on study # WBP/89/62) after drug administration plasma levels of GR 68755 increased with increasing dosages. Drug was not detected at 24 hr after drug administration, indicating no accumulation of drug after repeat administration.

Mean Plasma GR 68755 Base Concentrations (ng/ml)
45 Minutes After a Daily Oral Dose of
GR 58755C to the Dog. (Study D11865).



Error bars indicate +/- 1 standard deviation.

Fig. 1, Pg. 318, Vol. 1.23

Highest tested dose (20/30/25 mg/kg/day) produced CNS toxicities, increases in serum alkaline phosphatase (both sexes) and alanine aminotransferase activities (in males) without accompanying histopathological changes in liver and deaths. Mid dose level (5.5 mg/kg/day) could be considered as well tolerated dose since it only produced increases in plasma alkaline phosphatase levels (males: 68% and females: 34%).

12-Month Oral Toxicity Study in Beagle Dogs (Study # D12561)

Testing Laboratories: Glaxo Spa,
Verona, Italia

Study Started: June 10, 1991

Study Completed: July 5, 1995

GLP Requirements: A Statement of Compliance with GLP regulations was included.

Animals: Beagle dogs (about 4 months old, males = 5.5-8.1 kg and females = 5.1-7.2 kg).

Drug Batch No.: M91/025, M91/026 and M91/027.

Methods: Groups of dogs (4/sex/group) were given orally (capsules) GR 68755 at daily doses of 0 (placebo in gelatin capsules), 1, 5 and 20 (day 1-3)/25 (day 4 onward) mg/kg/day for 12 months. Additionally, dogs were included in control (2/sex) and high (2 males and 1 female) dose group for 6-week recovery study. Dosing was carried out at approximately 1 hr after feeding. During the first half of the study dogs were given 35-45 g of food per kg and 25-35 g food per kg subsequently. All dogs were observed for clinical signs 3-4 times daily. Body weights were recorded weekly and food intakes daily. Ophthalmic examinations and ECG recordings were performed on all dogs once pre-test, during weeks 14, 25 and 54 of the study. Hearing acuity tests were performed on all dogs during weeks 49, 53 (including otoscopic examination), 55, 56, 57 and 58 of the study. Blood samples were collected from jugular vein at pre-test and during week 14, 26, 52 and 59 of the study for hematology and serum chemistry tests. Overnight urine samples were also collected at pre-test, during week 14, 26, 52 and 59 of the study for urinalysis. Blood samples were also collected from jugular vein on days 1 (0, 0.25,

0.5, 0.75, 1, 1.5, 2 and 24 hr after drug administration), 37 (0, 2 and 3 hr after dosing) and at 0 and 2 hr after dosing on days 100, 184, 198 and 352 of the study for measuring drug absorption according to methods. At the end of study/recovery period all surviving dogs were sacrificed and subjected to complete necropsy and histopathological examinations. Additionally, right cochlea were also examined by

Results:

1. **Observed Effects**: Highest tested dose produced CNS toxicities (salivation, chewing, blinking, a rotating motion of the head, ataxia, stiff limbs and walking on tip-toe, abnormalities of movement and respiration, emesis and subdued behavior) in dogs.

2. **Mortality**: Two out of 6 females from high dose group died on days 37 and 39 of the study. Prior to death, these dogs showed severe CNS toxicities (tremors, convulsions, cyanosis and mydriasis) and these deaths were treatment related.

3. **Body Weights/Food Consumptions/Water Consumptions**: The initial and final mean body weights of control males were 6.70 kg and 13.71 kg and the corresponding mean weights of control females were 6.42 kg and 11.86 kg respectively. Food consumptions in control males and females were g/kg/day during the first half of the study and g/kg/day last half of the study. No treatment related effects were seen in treated males. In females, body weight gains were reduced by 8.6%, 0% and 5.4% in low, mid and high dose respectively, compared to control values (final body weights were 9%, 2% and 7% lower than the final body weights of the control group dogs). Food intakes were not significantly affected by the treatment.

4. **Hematology/Coagulation/Bone Marrow**: No treatment related effects were seen.

5. **Blood Chemistry/Urinalysis**: No treatment related effects were seen. At the end of treatment period, urinary volumes were increased by 158% and 186% in mid and high dose treated females respectively, without any significant changes in specific gravity. At the end of recovery period no such changes were evident.

6. **Vital Signs/Physical Examination/Ophthalmic Examination/ ECG/Hearing Tests**: No treatment related effects were seen. Hearing test were conducted by the sponsor (Glaxo Group Research Ltd., Hertfordshire, UK). indicated that hearing threshold at high dose level was "increased". At the end of recovery period hearing threshold returned to normal.

7. **Organ Weights**: No treatment related effects were seen.

8. **Gross Pathology**: No treatment related effects were seen.

9. **Histopathology**: No treatment related effects were seen.

10. **Electron Microscopic Examination of Cochlea**: No treatment related effects were seen.

11. **Plasma Level of GR 68755 (Report # WPT/92/325)**: Levels of GR 68755 were measured by At 2 hr after drug administration, plasma levels of GR 68755 increased with increasing dosages. At 24 hr after drug administration plasma levels of GR 68755 were below detection limit (ng/ml). Hence, there was no accumulation of drug after repeat dosing.

Table 1 Mean Plasma Concentrations (ng/mL) and (SD) in dog plasma, two hours after doses of 1, 5 or 25mg/kg daily (D12561)

Dose	Week 1	Day 37	Day 100	Day 198	Day 352
1mg/kg	68 (27)	65 (13)	80 (24)	86 (41)	89 (35)
5mg/kg	411 (71)	465 (97)	550 (172)	577 (225)	637 (214)
25mg/kg	3030 (1030)	4090 (316)	4520 (497)	4810 (646)	4530 (1130)

Table 1, Pg. 352, Vol. 1.24

Highest tested dose (20/25 mg/kg/day) produced CNS toxicities, "increased hearing threshold" (which at the end of recovery period returned to normal) and deaths. Mid dose level (5 mg/kg/day) could be considered as well tolerated dose since it only produced increase urinary volumes (158%) in females without any significant changes in specific gravity.

SPECIAL TOXICITY STUDY:

Evaluation in Female Guinea-Pigs of Potential Skin Irritancy Resulting From a Single Occluded Dermal Application
(G12367)

Methods: To assess the potential irritation on the skin, GR 68755 was applied to the skin (intact and abraded) of both flanks at 0 and 50% w/w suspension in soft/liquid paraffin under occlusive dressing for ~21 hours. After 21 hours the occlusive dressing was removed and the skin was examined at 24 and 48 hours after the treatment. Calcium chloride (20%) was used as a positive control.

Results: The results indicated that treatment with 50% w/w suspension of GR 68755 produced no irritant skin reactions. Treatment with calcium chloride significantly increased skin fold thickness on both intact and abraded skin.

Acute Eye Irritation Test in Rabbits
(L12445)

Methods: To assess irritant effects of GR 68755 on the rabbit eye, a single application of 10 mg GR 68755 to the eye of the New Zealand White rabbits. The ocular irritation was assessed approximately 1, 3, 6, 24, 48, and 72 hours after treatment.

Results: The results indicated that application of GR 68755 produced a slight corneal, moderate iridal and moderate conjunctival reactions. These reactions were reversible and all treated eyes appeared normal on day 7.

Evaluation of Contact Sensitizing Potential in Female Guinea-Pigs (G12434)

Methods: Female guinea-pigs were treated topically with 10% w/w GR 68755 at flanks on days 1, 3, 5, 8, 10, and 12 (induction). Freund's complete adjuvant was injected intradermally to separate adjacent sites on the same occasions. On day 30, these animals were treated topically with 10% w/w GR 68755 (challenge), and the skin reactions was assessed on day 31.

Results: The results indicated that none of the treated animals had positive reactions to the challenge.

29-Day Oral Toxicity Study to Assess the Effects on Hearing in Dogs (D20192)

Methods: GR 68755 increased hearing thresholds at 25 mg/kg at 48 weeks after treatment in the 52-week oral toxicity study in dogs. To assess the effects of GR 68755 on hearing following treatment with GR 68755 for a shorter period, GR 68755 was given orally to dogs at 0 or 20 mg/kg for 3 days and then the treated animals received GR 68755 at 25 mg/kg for 2 days. The animals were not treated during days 4-6 due to mortality on days 3 and 4 (1 found dead and 2 sacrificed). During days 7 through 15, the animals were dosed at 20 mg/kg/day. Another animal was sacrificed on day 15 due to increased body temperature and unsteady gait. Therefore, the dose of 20 mg/kg was reduced to 15 mg/kg for the rest of the study. All animals were observed for clinical signs of toxicity, body weight and food consumption, gross pathology and limited histopathology. Hearing test was performed before treatment, on days 3, 16, 23, and 30. Plasma level of test drug was determined on day 29.

Results: The results indicated that treatment with GR 68755 did not alter the hearing thresholds. The doses of 20 and 25 mg/kg/day were lethal. One female treated at 25 mg/kg was found dead 6 hours after dosing. Two males treated at 25 mg/kg were pyrexic with unsteady gait and one had convulsions and these animals were sacrificed on day 4. One animal treated at 20 mg/kg had increased body temperature and unsteady gait and was sacrificed on day 15.

Following clinical signs of toxicity were also observed in the animals treated at 25 mg/kg: open mouth, licking lips, and glazed eyes. The major treated related clinical sign of toxicity was dilated pupils. Decreased body weight and food consumption were noted in the treated animals.

CARCINOGENICITY:

13-Week Oral (via drinking water) Toxicity Study in Mice (Study # M12419)

Testing Laboratories: Pathology and Toxicology Division
Glaxo Group Research Ltd.
Hertfordshire, UK

Study Started and Completed: September 17, 1990 and June 2, 1992

GLP Requirements: A Statement of Compliance with GLP regulations was included.

Animals: $B6C3F_1$ mice (males: 25.0-32.7 g and females: 18.4-25.3 g)

Drug Batch No.: C1026/120/1

Methods: In this study dose selection was based on the results of 14-day palatability study (# M12418) in which mice were given water containing 0 (acidified water, pH 5.5), 0.005-0.007 or 0.5 mg/ml of GR 68755 to drink. A concentration of 0.5 mg GR 68755/ml caused reduction in water consumptions by 16% and 29% in males and females respectively. Based on water consumption data males were exposed to 65 mg/kg of GR 68755 and females were exposed to 70.5 mg/kg of GR 68755. According to sponsor, "the maximum palatable concentration is defined as a concentration that causes a decrease in water consumption of approximately 20% compared to control data". Based on the above findings, a concentration of 0.5 mg GR 68755/ml was considered to be maximum palatable in drinking water for $B6C3F_1$ mice.

Groups of mice (15/sex/group) were given (via drinking water) GR 68755 at daily doses of 20, 30 and 40 mg/kg/day (GR 68755 concentrations in drinking water were 0.11-0.13, 0.18-0.27 and 0.27-0.35 mg/ml respectively) for 13 weeks. The target dosages were achieved by varying the concentration of GR68755 in drinking water twice weekly, and the degree of adjustment depending on changes in mean body weight and water consumption during the previous measurement period. Control mice received acidified (pH 5.5) water. All animals were observed for clinical signs twice daily. Body weights were recorded weekly and water intakes were recorded twice weekly. Blood samples were collected from vena cava just before sacrifice to measure drug levels in plasma. At the end of study period, all surviving animals were sacrificed and subjected to complete necropsy. Only brain, kidneys, lungs, testes, heart, liver, spleen and ovaries from control and high dose groups were examined microscopically.

Results:

1. **Observed Effects**: None.

2. **Mortality**: None.

3. **Body Weight/Food Consumption/Water Consumption**: The initial and final mean body weights of control males were 28.9 g and 41.1 g and the corresponding mean weights of control females were 21.6 g and 27.8 g respectively. Food consumptions were not reported. Treatment had no consistent effect on body weight gains. In males, body weight gains were reduced by 6.3%, 1.4% and 3.5% at low, mid and high dose respectively, when compared to control values. In females, body weight gains were not affected by the treatment. Water consumptions in males were not affected by the treatment except in low dose group significant increase (8-37%) in water intakes were recorded. However, in treated females water intakes were decreased steadily over the treatment period such that, by the end of treatment period, water intakes were 12%, 11% and 22% lower than the control values in low, mid and high dose groups respectively.

4. **Hematology/Coagulation/Bone Marrow**: Not done.

5. **Blood Chemistry/Urinalysis**: Not done.

6. **Vital Signs/Physical Examination/Ophthalmic Examination**: Not done.